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RESPONSES TO ACUTE CARBON
MONOXIDE POISONING

A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE BIOLOGICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF DOCTOR
OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY

1936

By
NATHAN RONALD BREWER

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BLOOD-PRESSURE RESPONSES TO ACUTE CARBON MONOXIDE POISONING¹

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In some preliminary experiments, in which we were interested primarily in carotid sinus reflexes, we noted that administered carbon monoxide produced no rise in blood pressure.

Carbon monoxide acts as an asphyxial agent by combining with hemoglobin. This was first shown by Claude Bernard in 1857. J. B. Haldane (1895a) showed that carbon monoxide could act in no other way. A mouse given sufficient carbon monoxide to saturate all of its hemoglobin was quite normal when subjected to a pressure of two atmospheres of oxygen. A cockroach, representing an animal containing no hemoglobin, remained quite normal in an atmosphere of 80 per cent carbon monoxide and 20 per cent oxygen. Peters and Van Slyke (1931) sum up the evidence by stating that the action of carbon monoxide in doses sufficient to kill "is entirely an affair of the blood, and that there is no evidence that intoxication of the tissue cells occurs except from lack of oxygen." Furthermore, as is well explained by Barcroft (1932) and by Peters and Van Slyke (1931), carbon monoxide prevents the dissociation of oxygen from oxyhemoglobin at low oxygen tensions, such as exist in the capillaries. Thus we would expect the symptoms of carbon monoxide poisoning to be similar to those of anoxic anoxia, such as that produced by pure nitrogen administration but, because of the effect of carbon monoxide on oxyhemoglobin in the capillaries, we would expect them to be more severe. J. B. Haldane (1895b) drew a direct parallel between the physiological effects of the oxygen lack of altitude and that of carbon monoxide degree for degree, using oxygen content of blood as the measuring stick.

The work of Mares (1903), Hill and Flack (1908), and Mathison (1911) showed that a rise of blood pressure follows the onset of oxygen lack uncomplicated by carbon dioxide accumulation. But the work of Sollmann and Pilcher (1911) led to opposite conclusions. Recent work dealing with the carotid sinus (Bouckaert, Dautrebande and Heymans, 1930; Heymans and Bouckaert, 1932; Schmidt, 1932; and Heymans, Bouckaert,

¹ The present investigation was aided in part by a grant to the University of Chicago from the Rockefeller Foundation.

and Regniers, 1933) leaves no doubt that the original finding of Mares was correct. The results of Sollmann and Pilcher, then, remain unexplained. These workers used decerebrate curarized dogs which were kept alive by continuous insufflation of oxygen. They produced asphyxia by stopping the flow of oxygen and they produced anoxemia without increasing the carbon dioxide content by the substitution of a steady flow of illuminating gas (probably containing 30 per cent to 40 per cent carbon monoxide) for the oxygen.

In view of the above facts it was felt that any study of the differences in physiological responses between anoxic anoxia and the anemic anoxia produced by carbon monoxide would be of value. Therefore these experiments were designed.

METHODS. Dogs were used in all experiments. Nembutal, 35 mgm. per kilogram intraperitoneally, or barbital, 200 mgm. per kilogram. intravenously was used for anesthesia. In some cases it was necessary to supplement barbital with some ether during the operative procedure, but in these cases at least two hours elapsed after the ether was taken away before proceeding with the experiment.

A tracheal cannula was inserted for administration of gas mixtures. Blood pressure was recorded from one femoral artery while the opposite femoral artery was exposed for the taking of arterial blood samples.

Gas mixtures were given as indicated in the following series of experiments:

Experiments 1 to 5 inclusive.....	Pure nitrogen
Experiments 6 to 8 inclusive.....	Pure nitrogen in dogs that have had their carotid sinuses denervated and their vagi sectioned
Experiments 9 to 15 inclusive.....	Pure carbon monoxide
Experiments 16 to 18 inclusive.....	10 per cent carbon monoxide and 90 per cent oxygen
Experiment 19.....	50 cc. carbon monoxide per kilogram
Experiment 20.....	40 cc. carbon monoxide per kilogram
Experiment 21.....	15 cc. carbon monoxide per kilogram
Experiments 22 to 29.....	10 per cent carbon monoxide and 90 per cent air
Experiment 30.....	5 per cent carbon monoxide in nitrogen
Experiments 31 and 32.....	10 per cent carbon monoxide and 90 per cent nitrogen

The carbon monoxide was generated by allowing formic acid to drop from a separatory funnel into a flask of sulphuric acid heated in a water bath to 100 degrees. The generated gas was made to pass through a gas absorption tube containing a solution of NaOH to absorb what little carbon dioxide may have been generated along with the carbon monoxide, and the carbon monoxide was then collected over water in an aspirator

bottle. Tank nitrogen and tank oxygen purchased from the Air Reduction Company, Chicago, were used. Gas mixtures were placed in a Bailey

TABLE 1
Blood pressure changes and analyses of blood samples

EXPERIMENT NUMBER	CONDITIONS OF EXPERIMENT	CO CONTENT IN VOLUMES PER CENT		BLOOD PRESSURE PER CENT OF CHANGE FROM CONTROL AT TIME OF TAKING SAMPLE		O ₂ CONTENT IN VOLUMES PER CENT			CO ₂ CONTENT MILLIMOLES PER LITER ON WHOLE BLOOD		
		b	c	b	c	a	b	c	a	b	c
1	N ₂ -normal	—	—	-23	—	11.9	0.8	—	—	—	—
2	N ₂ -normal	—	—	+13	—	19.4	2.1	—	—	—	—
6	N ₂ -denervated	—	—	-60	—	15.3	2.6	—	—	—	—
7	N ₂ -denervated	—	—	-35	—	—	1.8	—	—	—	—
8	N ₂ -denervated	—	—	-10	—	—	1.5	—	—	—	—
9	Pure CO	21.1	17.1	-35	-10	19.3	0.9	3.5	—	—	—
10	Pure CO	15.3	11.3	-28	0	16.1	3.7	7.2	21.6	21.2	22.1
11	Pure CO	23.4	—	-63	—	23.8	1.1	—	—	—	—
12	Pure CO	17.0	—	-12	—	17.8	0.5	—	—	—	—
13	Pure CO	13.5	8.3	-28	-7	19.5	6.7	11.4	—	—	—
14	Pure CO	19.5	15.9	-35	0	19.0	0.8	4.3	—	—	—
15	Pure CO	19.4	—	-32	—	14.5	2.5	—	—	—	—
16	10% CO + 90% O ₂	18.0	17.6	-12	+10	22.2	3.9	4.6	15.4	15.8	19.2
17	10% CO + 90% O ₂	19.4	18.3	-23	-10	22.5	4.8	7.4	17.0	16.8	16.8
18	10% CO + 90% O ₂	17.0	—	-42	—	18.3	3.6	—	—	—	—
22	10% CO in air	23.4	24.4	-5	-5	20.4	2.0	2.0	15.3	14.2	13.4
23	10% CO in air	18.1	16.9	-35	+10	17.3	1.6	4.0	16.9	17.3	17.1
24	10% CO in air	20.0	17.5	-25	+60	25.2	4.5	8.3	8.0	10.2	11.8
25	10% CO in air	21.5	21.1	-17	+17	19.5	2.0	2.4	18.6	16.8	17.2
26	10% CO in air	19.2	17.8	-22	+5	17.1	1.3	3.5	17.3	14.4	15.5
27	10% CO in air	17.7	—	+10	—	17.6	4.4	—	13.3	15.1	—
28	10% CO in air	22.3	18.9	-43	+10	21.1	0.7	4.3	17.5	16.9	17.1
30	5% CO + 95% N ₂	12.6	—	+20	—	10.4	1.5	—	18.0	13.6	—
32	10% CO + 90% N ₂	20.9	—	-55	—	19.2	0.0	—	—	—	—

a indicates the first or "normal" blood sample.

b indicates the second or that sample taken during or just after gaseous administration.

c indicates the third or that sample taken on some critical point on the recovery curve.

(1921) gasometer of 100 liters capacity containing a counterbalance wheel to compensate for the weight of the bell when it was above water. Connections were made with $\frac{5}{8}$ inch copper tubing and with $\frac{5}{8}$ inch rubber tubing.

A T-connection was made close to the insertion of the tracheal cannula and two valves were used to direct the flow of air. The air from the outlet valve was led up a draft flue. In those experiments in which we used definite amounts of carbon monoxide plus oxygen we administered the gas in a closed system, adding oxygen as necessary and absorbing the carbon dioxide as generated as done in the carbon monoxide inhalation method for the determination of blood volume (Chang and Harrop, 1928).

Amounts of 5 to 6 cc. of arterial blood were taken for analysis of oxygen content and carbon monoxide content and, in some cases, for hemoglobin content and for carbon dioxide content of whole blood. The oxygen and carbon monoxide expressed as volumes per cent and the carbon dioxide content expressed as millimoles per liter were determined by the method of Van Slyke and Neill (1924). When hemoglobin determinations were made the method of Palmer (1918) or the direct method, that of determinations of oxygen capacity by saturating blood with air (Stadie, 1921) and then determining the oxygen content, was used. The first blood sample was taken just before the gas mixture was turned on. The second sample was taken either just before or just after the gas mixture was turned off except where otherwise indicated. If the animal recovered an attempt was made to take a third sample at some critical point on the recovery curve.

RESULTS. The findings in those cases where pure nitrogen was administered (figs. 1 and 2)² to five normal dogs and to three dogs that had had their carotid sinuses denervated and their vagi cut confirm the findings of those who had previously worked on this subject. In an atmosphere of pure nitrogen, experiments 1 to 5 inclusive, those dogs that were not denervated showed blood pressure changes of 18 per cent to 75 per cent above the normal followed by a fall. Those dogs that had had their vagi cut and their carotid sinuses denervated (expts. 6, 7 and 8) showed no rise in blood pressure while breathing pure nitrogen but only a fall (fig. 2). Three of the normal dogs (dogs 2, 4, and 5) recovered on return to air,

² For convenience the experiments are identified by numbers. Numbers omitted from the table showing the blood analyses indicates either that no blood samples were taken for that experiment or that no analysis had been successfully completed. Letters *a*, *b* and *c* in the table indicate, respectively, the first or "normal" blood sample; the second, or that sample taken during or just after gaseous administration; and the third sample, or that sample taken on some critical point on the recovery curve. On the figures the time of taking the *a* sample is not indicated—it was always taken just before the experimental gas mixture was turned on. The time of taking the *b* sample is at the junction of the broken line (representing the duration of the administration of the gas mixture) and the solid line (representing access to air) in every experiment excepting two—experiments 27 and 30—where the time of taking this sample is indicated as follows 27*b* and 30*b*. When taken, the time of taking the *c* sample is indicated in each case as follows 10*c* or 13*c*.

two of these (dogs 2 and 5) after artificial respiration had been performed. The recovery was marked by another rise in blood pressure, a rise of 28 per cent, 63 per cent and 72 per cent respectively above the normal. Two of the denervated animals (dogs 7 and 8) were successfully revived with the aid of artificial respiration after they were made to breathe air and the blood pressure levels of these dogs surpassed their normal blood pressure levels by 18 per cent and 30 per cent.

In those animals in which pure carbon monoxide was administered a sharp drop in blood pressure was evidenced after the first or second breath taken (fig. 3). Of seven animals (dogs 9 to 15 inclusive) given this gas four recovered after the gas was turned off. One of these (dog 9) maintained a blood pressure level 10 per cent above that of the normal for about two minutes and returned in another minute to the normal level. In the other three animals that recovered (dogs 10, 13 and 14) a return to a normal or slightly super-normal peak was reached where it did not

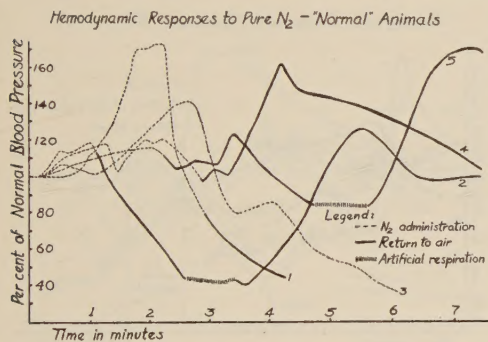


Fig. 1

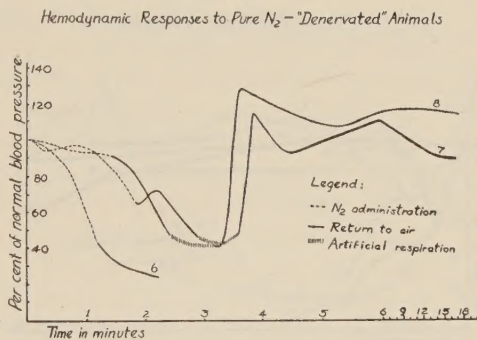


Fig. 2

remain but gradually dropped to a new level which it maintained for the duration of the observation.

Six animals were given mixtures of carbon monoxide and oxygen. Three of these (dogs 16, 17 and 18) were made to inhale a mixture of 10 per cent carbon monoxide and 90 per cent oxygen (fig. 4). The other three were given definite amounts of carbon monoxide per kilogram: 50 cc. of carbon monoxide per kilogram in experiment 19, 40 cc. of carbon monoxide per kilogram in experiment 20, and 15 cc. of carbon monoxide per kilogram in experiment 21. Drops in blood pressure were the only changes evidenced following the administration of the gas mixtures. Of three of these animals which were permitted to breathe air again before death one, dog 16, reached a supernormal blood pressure peak which then gradually dropped. The other two, dogs 17 and 18, did not again reach the normal blood pressure level.

Eight animals (dogs 22 to 29 inclusive) were given a mixture of 10 per

cent carbon monoxide and 90 per cent air (fig. 5). Of these, dogs 23 and 28 responded in the same manner as those given pure carbon monoxide or carbon monoxide plus oxygen, i.e., with a drop in blood pressure and, on return to air, a rise to a super-normal level followed by a gradual drop to a level below normal at which height it remained. The other six animals responded by a rise in blood pressure to about 10 per cent above the normal before dropping sharply. Three of these showed slight depressions before the rise. Five of the six dogs recovered—all reaching blood pressure levels above the normal.

In the group that had received a mixture of carbon monoxide plus nitrogen (dogs 30, 31, and 32; fig. 6) the response most nearly corresponded to that of pure nitrogen—there was a rise ranging from 15 per cent to 50 per cent above normal in all three cases followed by a fall. In one case, dog 31, where the fall had only gone to 8 per cent below normal at the time that the animal was returned to air there was a gradual rise on

Hemodynamic Responses to Pure CO

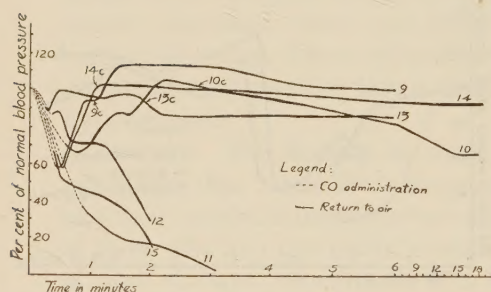


Fig. 3

Hemodynamic Responses to Mixtures of CO and O₂

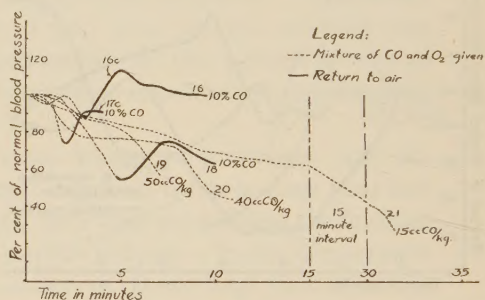


Fig. 4

recovery to 20 per cent above normal followed by a more gradual return to the normal level.

DISCUSSION OF RESULTS. As had been repeatedly shown the condition of anoxic anoxia such as that produced by the administration of an inert gas resulted in a rise of blood pressure followed by a fall when the carotid sinus and aortic depressor nerves were intact, and only a fall in blood pressure when the above mentioned nerves were eliminated. Those animals that recovered upon having access to air invariably showed a blood pressure response that rose to great heights above the normal. Hill and Flack (1908) also noted such rises in animals recovering from nitrogen administration. They state: "Upon the admission of air, the heart escapes from vagus inhibition, and beating with great force quickly drives the blood pressure to a height." It is obvious from our experiments that the release from vagus inhibition was not the sole cause of the sudden rise in pressure during recovery because the rise occurred in vagotomized animals. It is

probable that the rise was not due to carbon dioxide accumulation for there was no consistent rise in carbon dioxide content with the rise in blood pressure. It could not have been due to any latent effect on the carotid sinus and aortic depressor nerve endings because it occurred even when these were eliminated. There is some evidence (Kellaway, 1919a; 1919b) that anoxia can stimulate the adrenals to increase their output of adrenalin, but there is also evidence that the adrenals are not necessary for the rise in blood pressure in cerebral anemia (Rogoff and Coombs, 1923; Rogoff, 1924).

The failure of a rise in blood pressure to occur during carbon monoxide administration when this gas is administered with pure oxygen may be explained if we accept the evidence that the chief site of action in effecting the rise in blood pressure during the administration of pure nitrogen is at the carotid sinus and aortic depressor nerve endings. When pure oxygen supplements the carbon monoxide, although the oxygen content

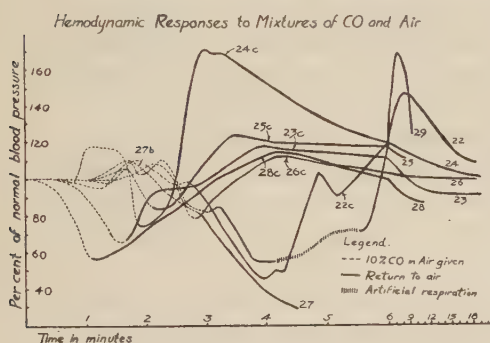


Fig. 5

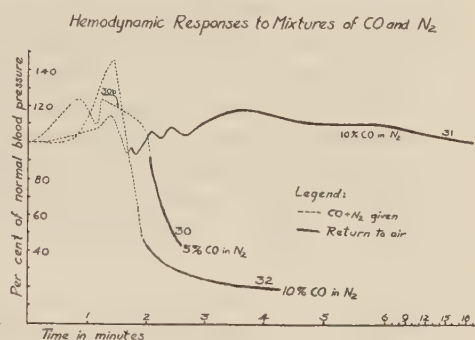


Fig. 6

of the blood in the arteries is greatly reduced, the oxygen tension is greatly increased and the aortic depressor and carotid sinus nerve endings, being among the first of the tissues to benefit from this increased oxygen tension, are permitted to draw on the oxygen freely so that, as far as those tissues are concerned, there is no anoxia and therefore no reflex effect resulting from anoxia.

The failure of a blood pressure rise to occur when pure carbon monoxide is administered is due to the toxic effect of pure carbon monoxide. It has been shown (Warburg, 1926; Haldane, 1927) that when the carbon monoxide tension reaches great heights it reduces tissue metabolism.

If the foregoing interpretations are correct then it should occasion no surprise to find that a rise in blood pressure is obtained when 10 per cent carbon monoxide and 90 per cent nitrogen are given. This procedure is necessary to show that the concentrations of carbon monoxide used are not necessarily poisonous to the carotid sinus and aortic depressor nerve

endings. It also supports the hypothesis that absence of a rise in blood pressure during the administration of carbon monoxide and oxygen is due to the oxygen dissolved in the plasma.

When carbon monoxide and air are used there may or may not be a rise in blood pressure. When a rise in blood pressure is observed the degree of the rise is not as great as that obtained during the administration of pure nitrogen or of nitrogen and carbon monoxide. The oxygen tension in the pulmonary vein is normal. It is conceivable that the tissues of the heart and the great vessels would draw on some of this limited supply of oxygen so that by the time the carotid sinus is reached the tension of the oxygen could be materially reduced—enough to cause a reflex rise in blood pressure at times.

SUMMARY AND CONCLUSIONS

It is generally assumed that the physiological responses of carbon monoxide poisoning in doses sufficient to produce any effect is alike in all respects to the effects of anoxic anoxia (Peters and Van Slyke, 1931). We have found, to the contrary, that animals given mixtures of *carbon monoxide and oxygen* do not respond by a rise in blood pressure, which is an invariable result of nitrogen administration. The absence of the rise is not due to any lack of capacity of the carotid sinus and aortic depressor nerve endings to receive stimuli because when the same concentration of *carbon monoxide is given with pure nitrogen* rises in blood pressure are obtained.

Animals recovering from anoxia produced in various ways usually attain blood pressure levels for a time greatly above the normal. The increased pressure is not due solely to release from vagal inhibition as has been stated (Hill and Flack, 1908) because it occurred as well in vagotomized animals.

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